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DOI: <https://doi.org/10.1136/esmoopen-2018-000481>

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ZORA URL: <https://doi.org/10.5167/uzh-169288>

Journal Article

Published Version



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Originally published at:

Bühler, Silja; Ramharter, Michael (2019). Flucelvax Tetra: a surface antigen, inactivated, influenza vaccine prepared in cell cultures. ESMO Open, 4:e000481.

DOI: <https://doi.org/10.1136/esmoopen-2018-000481>



Flucelvax Tetra: a surface antigen, inactivated, influenza vaccine prepared in cell cultures

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To cite: Bühler S, Ramharter M. Flucelvax Tetra: a surface antigen, inactivated, influenza vaccine prepared in cell cultures. *ESMO Open* 2019;4:e000481. doi:10.1136/esmoopen-2018-000481

Received 14 December 2018
 Accepted 15 December 2018

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On 18 October 2018, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion on the inactivated cell-based quadrivalent influenza vaccine Flucelvax Tetra for the use in adults and in children aged 9 years and above.¹ Influenza is a major cause of illness and mortality worldwide. Clinical attack rates often range from 10% to 20% in the general community during epidemics and can be as high as 50% in closed populations, such as schools or nursing homes.² According to the WHO, influenza causes annually three to five million cases of severe respiratory tract infections and is estimated to result in 290 000–650 000 respiratory deaths per year globally.³ During pandemics, such as the 1918 pandemic, the death toll has been estimated to be as high as 40 million.² Vaccination against influenza does not confer complete protection but it has been consistently shown to have an important impact on morbidity and has therefore become an important public health intervention to protect vulnerable patient populations. Since many years several commercial influenza vaccine products are available in Europe, so that one have to ask what are the advantages of the latest registered influenza vaccine compared with the available products?

The main difference between Flucelvax Tetra and traditional influenza vaccines lies in the production process of the vaccine. Until today, influenza vaccine production is mostly performed on embryonated chicken eggs. This production process however holds several disadvantages. First, a vast amount of eggs is necessary for production of global supply (about one egg per influenza vaccine dose) and fabrication therefore relies on adequate egg supply. In the case of an influenza pandemic, vaccine production can therefore not be scaled up rapidly. In contrast, Flucelvax production does not involve embryonated eggs but relies on cell culture. Cells used to manufacture Flucelvax can be kept

frozen and stored in cell banks. Storage in cell banks allows cell supply on a large-scale for a quick scale-up of vaccine production.⁴ In addition, the long timeline for production of egg-based vaccines has other important influenza-specific disadvantages: due to the long production process the target antigens for the next influenza season need to be defined many months before the next transmission period leading to a potential mismatch of the seasonal influenza strain and those selected for the vaccine.

Moreover, growing influenza viruses in eggs can introduce egg-adapted changes, rendering the vaccine-contained strain less similar to the actually circulating influenza strain. As the cell-based vaccine does not introduce these changes, the cell-based influenza vaccine potentially offers improved protection compared with the classical, egg-based influenza vaccine although evidence for this assumption is still limited.^{5,6} Finally, use of cell-based produced vaccine does not impose a risk to individuals allergic to egg protein.

Interestingly, the MDCK cell-based influenza vaccine was already introduced in Europe in 2007. Since whole intact MDCK cells were shown to be cancerogenic in rodents, this preclinical finding led to important reservations in the general population and medical community against the use of this cell based vaccine. Despite the fact that intact cells were completely removed during the manufacturing process of the vaccine and a positive opinion on the safety of this product was issued by the European regulators, market uptake of this vaccine was apparently unsuccessful leading to a subsequent withdrawal from the European market.^{7,8} Flucelvax Tetra has been licensed in the USA since 2016 and is similarly produced on MDCK cells. No relevant safety concerns have emerged since its introduction in the USA and it will be of interest whether market uptake will this time be positive in Europe.

The newly registered influenza vaccine Flucelvax Tetra consists of influenza virus surface antigens of four different strains (two A subtypes and two B subtypes). This is an important advantage compared with trivalent vaccines as it covers two B subtypes. Flucelvax Tetra is described to induce similar immune responses compared with previously licensed trivalent cell-based vaccines,⁹ which have been proven to be highly immunogenic in individuals ≤60 and >60 years of age.¹⁰ Immune responses are also considered to be similar to egg-based influenza vaccines. The most common local and systemic side effects were of expected nature (injection site pain, erythema induration, headache, fatigue, myalgia). Flucelvax Tetra is intended to be launched for the 2019/2010 season in Europe.

Individuals at highest risk for severe disease and complications are, among other groups, individuals with chronic medical and/or immunosuppressive conditions (eg, persons on chemotherapy or with a malignancy). A recent Cochrane Review on influenza vaccination in immunosuppressed adults with cancer concluded that the identified observational studies showed lower rates of infection-related outcomes and decreased mortality in patients with influenza vaccination.¹¹ Therefore, influenza vaccination is specifically recommended in these vulnerable patient groups and their contacts. Frustratingly, vaccination rates have been found to be alarmingly low in patients with oncological conditions—a population which might benefit disproportionately from seasonal influenza vaccination. Importantly, vaccination denial is based mostly on unjustified fears of potential side effects and interaction with malignant disease.¹²

Whether it is the classical egg-based influenza vaccine or cell-based vaccine—as physicians it is our duty to promote influenza vaccination particularly so in vulnerable patient groups such as patients with malignancies. Let us thus vaccinate our patients and also vaccinate their close contacts to confer herd immunity for those most benefitting from influenza vaccination! This requires to repeatedly inform patients and their relatives—as well as improving vaccination coverage in healthcare personal caring for this vulnerable patient population such as ourselves as treating physicians!

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Commissioned; internally peer reviewed.

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REFERENCES

1. European Medicines Agency, 2018. Meeting highlights from the Committee for medicinal products for human use (CHMP) 15-18 October 2018. Available from: <https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-15-18-october-2018> [Accessed 4 Dec 2018].
2. Heymann DL. Control of Communicable Diseases. In: Heymann D, ed. Washington D.C. USA: American Public Health Association, 2008: 402–8.
3. World Health Organization, 2018. Influenza (seasonal). Available from: [http://www.who.int/news-room/fact-sheets/detail/influenza-\(seasonal\)](http://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)) [Accessed 4 Dec 2018].
4. The Centers for Disease Control and Prevention, 2018. Cell-based flu vaccines. Available from: <https://www.cdc.gov/flu/protect/vaccine/cell-based.htm> [Accessed 4 Dec 2018].
5. Schild GC, Oxford JS, de Jong JC, *et al.* Evidence for host-cell selection of influenza virus antigenic variants. *Nature* 1983;303:706–9.
6. Robertson JS, Naeve CW, Webster RG, *et al.* Alterations in the hemagglutinin associated with adaptation of influenza B virus to growth in eggs. *Virology* 1985;143:166–74.
7. Omeir RL, Teferedegne B, Foseh GS, *et al.* Heterogeneity of the tumorigenic phenotype expressed by Madin-Darby canine kidney cells. *Comp Med* 2011;61:243–50.
8. European Medicines Agency (EMA), 2007. Scientific discussion - Optaflu. Available from: https://www.ema.europa.eu/documents/scientific-discussion/optaflu-epar-scientific-discussion_en.pdf [Accessed 4 Dec 2018].
9. Bart S, Cannon K, Herrington D, *et al.* Immunogenicity and safety of a cell culture-based quadrivalent influenza vaccine in adults: a phase III, double-blind, multicenter, randomized, non-inferiority study. *Hum Vaccin Immunother* 2016;12:2278–88.
10. Loebermann M, Fritzsche C, Geerdes-Fenge H, *et al.* A phase III, open-label, single-arm, study to evaluate the safety and immunogenicity of a trivalent, surface antigen inactivated subunit influenza virus vaccine produced in mammalian cell culture (Optaflu®) in healthy adults. *Infection* 2018;16.
11. Bitterman R, Eliakim-Raz N, Vinograd I, *et al.* Influenza vaccines in immunosuppressed adults with cancer. *Cochrane Database Syst Rev* 2018;2:CD008983.
12. Poepl W, Lagler H, Raderer M, *et al.* Influenza vaccination perception and coverage among patients with malignant disease. *Vaccine* 2015;33:1682–7.